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Chapter

Biological Therapy in the Prevention of Complications of Crohn

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Abstract

In recent years, the advent of biological agents has revolutionized the treatment of inflammatory bowel disease (IBD). TNF is a cytokine with a very important role in the pathogenesis of Crohn's disease (CD), so it is a therapeutic target to highlight. The efficacy and safety of the anti-TNF, IFX and ADA is widely established, becoming two of the therapeutic pillars of CD. Today the experience with other more recent antibodies and stem cells therapy is more limited. Various limitations such as lack of studies, heterogeneity in inclusion criteria, and achievement of objectives make it difficult to establish which treatment is more appropriate in each case and even the superiority between drugs and/or cellular therapy. This chapter will compare the different currently available therapies with special interest in new therapies and their relationship in the prevention of complications of Crohn's disease.

Keywords: Crohn's disease, fibrosis, inflammation, biological therapy, inflammatory bowel disease, stem cells

1. Introduction

Acute inflammatory processes affecting the intestine are relatively frequent and self-limiting, such that the intestinal mucosa is able to regenerate and regain homeostasis in a matter of days. However, chronic inflammation can cause irreversible structural changes and severe complications in the gastrointestinal tract [1].

The term inflammatory bowel disease (IBD) is used to refer generically to chronic inflammatory diseases, with recurrent course and unknown origin that affect the gastrointestinal tract and are distinguished mainly on the basis of histological findings. Basically in this group we find Crohn's disease (CD) and ulcerative colitis (UC), processes that have their peak incidence in young people and that constitute the most relevant pathologies within this classification. These pathologies are identified and diagnosed thanks to clinical, endoscopic, and histological characteristics, although on certain occasions it is not possible to distinguish which form of IBD is present, being classified as indeterminate colitis. Microscopic colitis is a term designated for a group of colitis in which we find microscopic but not macroscopic alterations when endoscopy or surgery is performed. Unlike the previous ones, this process mainly affects elderly people and includes collagenous colitis and lymphocytic colitis. Despite having similar epidemiological, clinical, and

even therapeutic characteristics, there are a series of peculiarities that help to define the existing process [2]. CD is characterized by the existence of transmural inflammation, cryptic abscesses, and the formation of granulomas, being able to affect any part of the intestine and may reappear after surgical resection of the affected segment [3]. UC, on the other hand, is typically associated with inflammation and ulceration limited to the mucosa and submucosa, only of the colon and rectum. In this way, and unlike CD, UC has a definitive treatment of the pathology in proctocolectomy. The main differential characteristics between CD and UC are shown in **Table 1**. The incidence of both diseases is increasing in the last decades and in the case of CD at younger ages [4].

Current CD therapies are solely targeting inflammation by administration of immunosuppressive therapies, corticosteroids, or biologicals. While these therapies in some—but not all—cases lead to symptomatic disease remission, recurrent flares interspaced with periods of remission will still result in cumulative gut wall remodeling. The evolution towards organ failure and surgical resection occurs in 70% of cases, with a subsequent need of second surgery in up to 30% of cases [5]. The postsurgical recurrence can occur very early, even a few weeks after surgical

Characteristics	Crohn's disease	Ulcerative colitis
Macroscopic		
Intestinal region	Ileum ± colon	Colon
Distribution	Sautéed lesions	Diffuse lesions
Stenosis	Yes	No
Wall appearance	Thick	Thin
Microscopic		
Inflammation	Transmural	Limited to *mucosa*
Pseudopolyps	Moderate	Important
Ulcers	Depths	Superficial
Lymphoid reaction	Important	Moderate
Fibrosis	Important	Mild or absent
Serositis	Important	Mild or absent
Granulomas	Yes	No
Fistulas	Yes	No
Clinics		
Rectal involvement	Frequent	Almost always
Small bowel involvement	Frequent	Rare
Perianal fistula	Yes	No
Malabsorption of fats and vitamins	Yes	No
Malignant potential	Affecting the colon	Yes
Relapses after surgery	Frequent	No
Toxic megacolon	No	Yes
pANCA	+	++
ASCA	++	+

The table shows the main macroscopic, microscopic, and clinical characteristics between CD and UC.

Table 1.
Differential characteristics between CD and UC.

resection, because the drugs currently available for the prevention of postsurgical recurrence have limited efficacy; up to 50% of cases return to CD activity despite preventive treatment, which may lead to further surgery with consequent loss of bowel function which may eventually lead to the development of short bowel syndrome as an irreversible complication in some patients. Therefore, management of CD patients undergoing bowel resection should be oriented towards prevention, early detection, and, in the worst case, treatment of postsurgical recurrence [6].

Given the great evolution experienced in IBD therapy, there is a need to compare the effectiveness of different treatments in the achievement of objectives as well as a clear definition of the objectives. The symptoms, although an indicator of quality of life, have a very poor correlation with the severity of inflammation. On the other hand, endoscopic activity, serological markers, and fecal calprotectin have greater correlation with the future need for surgery and occurrence of complications.

Among the objectives of the therapeutics of IBD, we highlight the induction of remission, the reduction of hospitalizations and surgeries, and the effectiveness of cellular therapy in fistulizing and luminal disease.

The general objective of this chapter is to address this gap in literature by reviewing bibliography comparing the different biological therapies available and their influence on the prevention of complications.

2. Crohn's disease

CD is a chronic, recurrent inflammatory disease that belongs to the spectrum of IBD. It predominantly affects the gastrointestinal tract, being able to find lesions in any part of it, from the mouth to the anus. In it we also find important extraintestinal manifestations and association with other autoimmune diseases [7]. CD is an entity whose incidence increases as the development of society advances, being very prevalent in developed countries and rare in less developed countries.

The maximum incidence is observed between the second and fourth decade of life, and a second peak is observed between the seventh and ninth, although it is increasingly diagnosed at earlier ages [4].

2.1 Etiopathogenesis

Although several factors have been described that may be related to the development of CD, the exact causes of this process remain unknown (see **Table 2**).

Genetics	Seventy-one susceptibility locus for CD have been identified on 17 chromosomes
Environmental factors	Non-breastfeeding, improved hygiene conditions, sedentary lifestyles, western diet and fast food, tobacco, contraceptives, environmental pollution
Microbiota	Reduction of commensal microbiota: *Bacteroidetes* and *Firmicutes* Increase in potentially pathogenic flora: *Mycobacterium avium paratuberculosis*, *Campylobacter*, *Salmonella*, and *E. coli*
Alteration of the immune system	Deregulation in the immune system that initiates, mediates, and perpetuates inflammation. Rapid recruitment and inappropriate accumulation of leukocytes in the affected intestinal wall

The table shows the main causes of CD.

Table 2.
Etiopathogenesis of CD.

Several studies [8, 9] have found different genetic alterations that increase susceptibility to this disease along with certain environmental triggers, resulting in an altered immune response, both innate and adaptive, and epithelial bowel dysfunction. An alteration in the commensal microbiota has also been described, with a decrease in the potentially beneficial flora and an increase in that which is potentially pathogenic [8]. Genetic alterations, the immune system, microbiota, environmental factors, and their combined effects occupy a large number of pages in the scientific literature, and their description surpasses the objectives of this study.

2.2 Symptoms, diagnosis, and classification

CD is a heterogeneous entity comprising different phenotypes, so the symptoms are and change with the course of the disease. It usually has an insidious onset, the most common symptom being chronic diarrhea (80% of patients), followed by abdominal pain (70%), primarily in the right iliac fossa.

Other symptoms are weight loss (50%), malnutrition, fatigue, malaise, and the presence of rectorrhagia (more common in UC). Perianal disease (4–10% debut with it), nausea, vomiting, asthenia, anorexia, fever, and night sweats may also occur.

Diagnosis is currently established by combining clinical presentation and laboratory findings (such as anemia, elevation of globular sedimentation velocity and serum C-reactive protein, elevation of calprotectin and/or lactoferrin in stool, endoscopic appearance, histology, and radiological and/or biochemical findings). Serological and genetic tests are not recommended as routine diagnostic methods. However, despite advances in diagnostic methods, in the first year, up to 5% of cases with the diagnosis of CD has to be changed to UC or indeterminate colitis [10].

Once the diagnosis of CD is established, it is necessary to categorize patients based on the Montreal classification [11] and investigate the possible existence of extraintestinal manifestations and other autoimmune diseases (see **Table 3**). This stratification of patients makes it easier for them to receive the best follow-up and treatment in an individualized manner as well as to identify early possible complications [12]. However, it is important to bear in mind that the patient's stratification is not stable. It has been seen that 19% of patients progress to more aggressive forms of the disease 90 days after being staged and up to 51% of patients did so 20 years after the initial diagnosis [12]. These patients progressed developing complications that were not present at the time of diagnosis.

Age at diagnosis	A1:<16 years
	A2:17–40 years
	A3:>40 years
Location	L1:terminal ileum
	L2:colonic
	L3:ileocolon
	L4:upper gastrointestinal tract
Behavior	B1:without stricture formation, non-penetrating
	B2:stenosant
	B3:penetrating
	P:perianal disease

Table 3.
CD Montreal classification [11].

Complications depend on the clinical course and control of the disease. Some may appear in any phenotype, such as massive hemorrhage, toxic megacolon, and neoplasia of the colon (the IBD favors the presence of multiple tumors with a higher degree of malignancy), while other complications are encompassed in different phenotypes of the disease. Thus, in the obstructive fibro-stenotic pattern, we find stenosis, intestinal obstruction, and perianal disease; and in the penetrating, fistulas and abscesses.

Most complications require a surgical approach; in fact, 70–80% of patients with CD will need some surgery throughout their lives. Even so, there are recurrences in 88% of the cases, being very frequent the surgical reintervention.

2.3 Treatment

There are currently multiple drugs available for the treatment of IBD; however, there are no predictive response factors that allow us to select the most appropriate drug for a patient at any given time. In general, the choice of treatment is made on an individual basis according to the activity, location, and phenotype of the affectation.

The objectives include symptomatic control, remission of the outbreak and maintenance of long-term remission, as well as endoscopic healing, as there is no curative treatment. The drugs used are:

- *Aminosalicylates*: indicated as maintenance treatment in mild to moderate CD. They include those molecules with aminosalicylic acid or 5-ASA in their molecular structure (also known as mesalazine in Europe and mesalamine in the USA). They have been shown to reduce the incidence of relapses (28 versus 55% with placebo) and have a higher percentage of remissions versus placebo (43 versus 18%, respectively). However, the efficacy in postoperative patients is greater. In general, they are well tolerated, and adverse effects such as gastrointestinal disorders, headache, arthralgias, and cutaneous eruptions may appear. The nephrotoxicity and hematological toxicity are the more serious, but infrequent, effects [13, 14].

- *Glucocorticoids*: indicated for the induction of remission in an outbreak. They intervene on the vascular [decreasing permeability] and cellular [inhibiting tissue migration and phagocytosis of macrophages] phases. Prednisone is usually used at a dose of 40–60 mg/day orally or intravenously in severe outbreaks (with remission rates of 66–73%). Budesonide has shown similar efficacy to prednisone for mild to moderate ileocolonic CD (55% remissions). In addition, its topical action confers fewer adverse effects. However, they have not shown efficacy as a therapy for maintenance. In addition, this would be inadvisable given the risk of dependence and adverse effects: fluid retention, stretch marks, redistribution of body fat, subcapsular cataracts, myopathy, osteonecrosis, emotional disturbances, withdrawal symptoms, etc., many of which are related to the duration of treatment [15, 16].

- *Antibiotics*: have no role in the treatment of CD, except metronidazole in perianal disease.

- *Thiopurines*: azathioprine (AZA) and 6-mercaptopurine (6MP). They are used in the management of corticosteroid-dependent CD, in the prevention of postsurgical recurrence, and in combination with biologics. The efficacy is appreciated from 3 to 4 weeks both as maintenance therapy and in perianal

disease. They present a great interindividual variability, due to the genetic polymorphisms of TPMT (thiopurine methyltransferase), an enzyme that activates them. In general they are well tolerated, being hepatotoxicity, myelotoxicity and pancreatitis acute, the adverse effects to highlight, able to justify abandonment of the treatment. Other effects are nausea, fever, skin rash, hepatitis, and the development of lymphomas.

- *Methotrexate*: inhibitor of dihydrofolate reductase (folic acid antagonist). It is effective in maintenance of remission (65 versus 39% with placebo), with an evaluation necessary of hepatic enzymes. Hypersensitivity pneumonitis is a very rare but very serious adverse effect. Supplementation with folic acid reduces adverse effects. It is a teratogenic drug, so it is contraindicated during pregnancy and lactation [17].

- *Calcineurinics*: cyclosporine (CyA) and tacrolimus. Its usefulness is limited, although tacrolimus seems useful in perianal EC. CyA has a series of cases that support it in luminal and perianal EC, but the evidence is not robust.

- *Hematopoietic stem cell transplantation (HSCT)*: might be useful in some treatment-resistant cases. Mesenchymal stem cells (MSCs) have regenerative and immunomodulatory properties which lead to reduction of inflammation and healing of affected intestinal tissue in CD. Meta-analysis studies show that 23–40.5% of patients achieved remission after systemic infusion of MSCs [18, 19].

- *Monoclonal antibodies*: include the anti-TNF and anti-integrin α4β7, which we will discuss with more depth below.

3. Biological therapy in CD

Biologic therapy was introduced as a treatment for CD 20 years ago, revolutionizing the handling of it. So far, infliximab (IFX), adalimumab (ADA), vedolizumab (VDZ), and ustekinumab have been approved in Europe for this purpose. In general they have a good safety profile, although the experience is limited in new drugs.

They have been shown to be effective in decreasing intestinal damage from inflammation, surgeries, and admissions, improving the quality of life of patients. Its benefits, specially their early administracion as well as their favorable safety profile, have meant that they are being used more and more frequently.

It should be noted that before starting treatment with biological therapy, it is necessary to rule out an active infection (mainly tuberculosis or hepatitis B). In addition, the appearance of hypersensitivity reactions, cutaneous reactions, cytopenias, heart failure, and autoimmune hepatitis forces to rule them out and assess a possible interruption of treatment. Its paradoxical inflammatory reactions have been described with psoriasis and dermatitis, which can affect even 10% of patients. Treatment with biologics contraindicates attenuated vaccines.

Its potential adverse effects make it necessary to stratify the patients, so that only those with severe or complicated illness receive early intensive therapy. Although there is no established definition of serious or complicated disease, greater complications are seen in patients who start the disease young (<40 years), perianal disease and/or ileocolic localization, with need to administer corticosteroids in the treatment of the first outbreak, in these cases. When two or more factors are present, it is indicated to start the treatment of the first outbreak with immunomodulators or biologicals. Various studies support that, although the monoclonal

antibodies are more expensive than other treatments, the decrease in the number of hospitalizations and surgeries contributes to increase the cost/benefit ration of the therapy, especially as a therapy of the maintenance.

3.1 Anti-TNF

Anti-TNFs are so far the most effective agents in the treatment of moderate-to-severe luminal disease (induction of remission and maintenance) and Crohn's fistulizer, and they are the first-line treatment in complex perianal disease. In Europe, IFX and ADA are approved in EC and CU and golimumab in CU. The results obtained have raised treatment expectations, with healing of the mucosa being the main objective, associated with a lower rate of hospitalizations and surgery and with a higher percentage of long-term remission. Difficulty in selecting patients that are going to benefit from these treatments lies in safety problems (risk of infections, infections, etc.) and its high cost.

Anti-TNFs have demonstrated a good safety profile, the main drawback being the risk of infections, such as tuberculosis, pneumocystis, and nocardiosis. More than half of infections occur in the first 6 months of treatment and in guidelines combined with immunosuppressants. All of these risks justify the recommendation to update the vaccination schedule before starting treatment, as well as screening for latent infections [20].

The increased risk of cancer is controversial in the literature. A meta-analysis that included 12 cohort studies concluded that although the risk of melanoma is increased by 37% in patients with IBD, treatment with anti-TNF did not influence it [21].

Less frequently, they have also been associated with optic neuritis, seizures, and demyelinating disorders, including multiple sclerosis and exacerbation of heart failure symptoms grade III/IV. Adverse effects make it necessary to discontinue treatment in 20.6% of patients with IFX and 14.4% with ADA [22–25].

Another aspect to mention is the lack of effect (30%) and the loss of therapeutic efficacy, which occurs in 23–26% of patients in the first 12 months of treatment. The causes are varied: in some patients there is a pharmacodynamic failure, when the main pathway of inflammation is not dependent on TNF. Others do not get a good pharmacokinetics, when the concentrations in plasma are insufficient, due to increased clearance or appearance of anti-drug antibodies.

There is evidence that good plasma levels of anti-TNF are associated with greater clinical efficacy, so monitoring of antibody levels has become a tool to optimize the treatment. They appear more frequently in patients treated sporadically than those treated every 8 weeks. In these situations, it is possible to add immunosuppressants (AZA, 6-MP, or methotrexate).

3.2 Anti-integrin α4β7

Until 2015, anti-TNFs were the only biologicals approved for the treatment of IBD in Europe. This year anti-integrin α4β7 antibodies were incorporated: vedolizumab (VDZ) and ustekinumab. In general, they present an acceptable safety profile, as no case of leukoencephalopathy has been recorded to be progressive multifocal, its most fearsome adverse effect. As for the rest of the adverse effects, specific monitoring is not required.

Vedolizumab is a recombinant humanized IgG1 AcM that specifically blocks the integrin α4β7 by joining MadCAM-1. It has recently been approved for EC and moderate-to-severe CU that have failed conventional treatment but also as a first-line drug. It is administered via IV, for which it has demonstrated efficacy in inducing remission and maintaining disease, the maintenance in postoperatives

being its main indication. It has been postulated that its answer is slower because it does not block the pre-existing inflammation; it simply avoids recruiting more inflammatory cells. In addition, transmural involvement of CD may explain its action to be slower than CU.

The induction dose is 300 mg IV in weeks 0, 2, and 6, followed by 300 mg every 8 weeks as maintenance. A long-term loss of response has been noted, although usually in patients who have already failed other biologics. VDZ is a well-tolerated drug with a good security profile in IBD. The risk of infections increases but no cases of progressive multifocal leukoencephalopathy (PML), and the frequency of transfusion reactions is lower than that of the 5%. The development of anti-VZD antibodies occurred in less than 4% of patients, being a cause of therapeutic failure [26].

Natalizumab is a humanized IgG4 against the subunit α4, so it blocks both the integrin α4β7 and integrin α4β1; it therefore, has a non-specific action. It has shown promising results as maintenance therapy but has not been approved by its association with cases of progressive multifocal leukoencephalopathy. It is approved for CD in the USA under very severe conditions (concomitance with multiple sclerosis).

3.3 IL-12 and/or IL-23 inhibitors

IL-12 and IL-23 have been shown to be key cytokines in the adaptive immunity, which is found in IBD and intervenes in its chronification. Both ILs have in common the subunit p40, whose blocking inhibits the intracellular signaling cascade. The Crohn's immune response is influenced by resident lymphocytes and those recruited into the lymphoid organs. Antibodies from this group, such as the ustekinumab, prevent the binding of soluble IL-12 and IL-23 to their specific receptors, although they do not intervene on cytokines that are already attached to their membrane receptor. The blockage of IL-12 prevents the activation of Th1 lymphocytes, and IL-23 prevents the production of IFNγ, TNFα, IL-1β, and IL-6.

3.4 Sphingosine receptor modulators

Sphingosine-1 is a phospholipid that binds to specific receptors (S1P1–5) expressed in lymphocytes, dendritic cells, cardiomyocytes, and endothelial cells, regulating multiple cellular activities such as growth and survival, vascular integrity, and lymphocytic migration.

Sphingosine modulators behave like agonists producing functional antagonism, sequestering lymphocytes in peripheral lymphoid organs, and reinforcing the endothelial barrier (which makes intestinal migration difficult) [27].

3.5 JAK kinase inhibitors

Protein kinases are enzymes capable of modifying other proteins or enzymes, altering their function depending on the target. Certain polymorphisms of the same ones have been related with greater susceptibility to IBD. The signaling of this group of drugs is very complex, but it is a promising research in the field of IBD therapy (currently in phase 3 for both UC and CD).

In its mechanism of action, B lymphocytes and T effectors decrease without affecting the T regulators.

3.6 Biological therapy in the induction of remission

We speak of partial or total remission to refer to the reduction or disappearance of symptoms and signs of disease.

The effectiveness of biological therapy in the induction of remission is indisputable. However, the percentages vary considerably between different molecules. At week 4, remission rates reach 75% with IFX [28] and 59% with ADA [29].

The study PRECISE 1 investigated the effects of CTZ at week 6 and shows remission rates of 37% with CTZ and 31.4% for VDZ [30]. Clearly higher percentages are noticeable with IFX and ADA.

Considering luminal disease, remission rates have been described as 63.8 and 54.1% for IFX and ADA, respectively, and remission in cortico-dependent patients as 76.3 and 44.7% for IFX and ADA at 12 months. Combination with immunosuppressants led to higher remission rates in patients with IFX (81 versus 52%), but not in ADA [31].

In general, IFX is given to patients with a more severe phenotype of the disease, as it is believed to have faster action and more clinical experience. However, the results were similar in patients who received IFX and ADA, without finding significant differences in Crohn naïve patients except in the safety profile (adverse effects were more frequent with IFX than with ADA, 36.1 versus 15.5%, respectively), including transfusion reactions, skin rashes, arthralgias, and hypersensitivity [31]. This information is contradicted by other studies, such as the meta-analysis of Singh and collaborators, whose results support the superiority of IFX over the rest of the biologics for induction of clinical remission in naïve anti-TNF patients [32].

3.7 Impact of biological therapy in the prevention of complications of Crohn's disease

The effectiveness of biological therapy in the prevention of hospitalizations and surgeries has not yet been clearly demonstrated. We know from previous studies that in the prebiological era, approximately 50% of patients required surgery 10 years after diagnosis, with a risk of recurrence of 50% at 10 years, and 80% of patients required surgery at some point in their lives. Recent studies indicate that surgery rates since the introduction of biologics (2001–2008) are lower than those of 1988. In addition, a very relevant characteristic of biologics is their high cost, and it is here that the reduction of the overall cost through the prevention of complications becomes especially important [33, 34].

The anti-TNF therapy reduces significantly the hospitalizations and surgeries in patients with CD. No differences were observed between IFX and ADA, with a reduction of 46% (36–60%) of the hospitalizations and 13–42% of surgery with IFX. The onset of treatment may also be relevant in modifying the natural history of the disease. In this line, it has noted that early use of biological therapy (less than 2 years after diagnosis) improves the course of the disease. However, no significant reduction in the number of surgeries has been found in hospitalizations with patients treated with VDZ or AZA in similar follow-up periods [33].

4. Hematopoietic stem cell transplantation

Human stem cell therapy for the treatment of CD is still in its infancy, and whether SCT is associated with improved outcomes is unclear.

Preliminary studies have shown that allogeneic HSCT may restore, at a genetic level, the immune system [35, 36], and autologous HSCT could remove atypical clones by immunoablation and replacement with not committed stem cells (SCs), allowing for the de novo generation of an altered T-cell repertoire [37]. Some studies describe that autologous and allogeneic HSCT produce a long-term treatment-free disease regression in some patients with CD [19]. Nevertheless, the Autologous

Stem Cell Transplantation International Crohn's Disease Trial [38] did not validate a statistically significant improvement in continued disease remission at 1 year of autologous HSCT compared with orthodox therapy, suggesting that further studies are needed in order to know the feasibility of using HSCT in patients with refractory CD [19].

4.1 Luminal disease

The number of patients requiring surgical resection for the stenosing and uncontrolled inflammatory complications of CD has not declined significantly, despite advances in biological therapy. Moreover, following a surgical resection, many patients will require a second operation. Currently, the use of systemically infused mesenchymal stem cell to reduce the altered inflammatory response and to repair impaired tissue has a promising future for avoiding surgery and its potentially serious complications. Conversely, since biological therapies are not always useful in some patients, the development of all-purpose anti-inflammatory therapies for patients with inflammatory luminal disease is still needed.

In luminal disease, the mechanism of the intravenous transplantation of MSCs is not understood yet. Animal studies and graft-versus-host disease treated by bone marrow MSC studies suggest, on the one hand, that the MSCs are able to transmigrate from the circulation into the inflamed tissues as a response to cytokine stimulus; on the other hand, MSC can release anti-inflammatory cytokines, which can modify the phenotype of macrophages towards repairing phenotype and can mediate the activation and proliferation of regulatory T and B cells.

One study that demonstrated the safety and viability of MSC in luminal disease was evaluated in nine patients with refractory CD, where the patients received two infusions of autologous bone marrow-derived MSC (days 0 and 7). At 6 weeks, endoscopic improvement was reported in two patients and clinical improvement in three, while three patients required surgery due to worsening disease [39]. In the same line, similar results were also seen in 15 CD patients with moderate-to-severe active disease who were refractory to anti-TNFα therapy [40]. In that study, at 6 weeks, a clinical response was observed in 80% of patients, clinical remission in 53% of patients, and endoscopic improvement in 47% of patients [40].

Evidence that MSC therapy contributes to neoplastic development is currently lacking. However, this view is based on a systematic review in which not all patients were assessed by repeated endoscopy during the 10-year follow-up, so the presence of dysplastic lesions cannot be excluded [19]. New and better studies are needed to test the safety of MSC therapy in luminal disease.

4.2 Fistulizing disease

Fistulae commonly complicate CD. There has been more research on the efficacy of MSC therapy in perianal fistulizing CD than on luminal CD. In all cases, the reduction of fistula frequency and the improved rate of complete fistula closure are the most important therapeutic goals. Administration of the therapeutic agent is performed locally under general anesthesia during perianal surgery. In the intervention, the surgeon initially scans the fistula tracts to remove setons and residual inflamed tissues. Once the internal opening is sealed with absorbing suture, the submucosa surrounding the internal orifices of fistulas and parallel to the lumen of tracts receives an injection of MSCs. The difference between results depends on different parameters like used dosage, origin and type of MSCs, therapeutic schedules, definition of end points, and therapeutic efficacy.

The safety and therapeutic potential of MSCs in treating perianal CD was first demonstrated in 2005 when autologous adipose-derived MSC was injected into nine perianal fistulae from four patients. After 8 weeks, complete healing was observed in six fistulae [41]. Fistula tract healing has been observed in 71% of patients treated with MSC and fibrin glue as compared to 16% of patients treated with fibrin glue alone. In patients receiving MSCs, closure was observed in 46% of patients after a single treatment and in a further 25% after a second rescue treatment [42, 43].

The currently available largest randomized, double-blind placebo-controlled study summarizes the clinical data of fistulizing CD patients which show that a greater proportion of patients in the treated group than the placebo group achieved the combined remission at week 24 in the intent-to-treat population (53 of 103 (51%) vs. 36 of 101 (34%)) [44].

5. Conclusions

- The evidence places IFX over the rest of the biologics in the induction of remission in patients with naïve CD. It has shown higher remission percentages in numerous quality studies and in direct meta-analysis comparisons. While this information is contradicted by other articles, IFX seems to be more effective and faster acting, so it is the preferred biological therapy in patients with severe disease. In addition, it is the only one that has proven to be more effective in combination with immunosuppressants.

- The biological treatments are the only ones that have shown effectiveness in the reduction of hospitalizations and surgeries. A number of studies have highlighted the superiority of IFX over other biologicals, as well as the equivalence between ADA and CTZ.

- Clinical trials demonstrated that MSC transplantation has an outstanding, durable efficacy with low fistula recurrence in biological therapy-refractory fistulizing CD; however, further clinical trials are required to confirm its effectiveness in luminal CD.

Conflict of interest

The author declares no conflict of interest.

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